

AMENDMENTS TO THE CLAIMS

The claims and their status are reflected below. Claims 1-22, 28-30, 33, 44, 46, 58, 60, 65 and 66 are pending in the application.

1. (Currently amended) A method for analyzing a plurality of sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

providing for each of the plurality of genes a parameter that contains information concerning differences in the associated values of that gene among the sets;

adjusting the parameters of the plurality of genes so that variables related to the parameters are substantially independent of variations of scatter values or average associated values of the genes over the sets, said scatter values defined by standard deviation of the associated values in the sets;

deriving an observed value and an expected value of the adjusted parameter for each gene from the sets of associated values, said expected value being indicative of extent of variations in the adjusted parameter introduced by the process;

comparing the observed and expected values of the parameter to identify genes whose associated values differ by an amount of statistical significance among the sets; and

providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

2. (Previously presented) The method of claim 1, wherein said adjusting includes: dividing the scatter values or average associated values of the genes into subsets each having a similar range of values, and calculating the standard deviation of each of the parameters within each subset;

altering the parameters until a coefficient of variation of the standard deviations of the parameters among the subsets is minimized.

3. (Previously presented) The method of claim 1, further comprising obtaining said sets of associated values from multiple measurements of the plurality of genes, or values derived therefrom.

4. (Original) The method of claim 1, wherein said sets of associated values represent gene expression or number of gene copies or levels of protein encoded by the genes.

5. (Original) The method of claim 1, wherein said sets of associated values include calculated or predicted values.

6. (Previously presented) The method of claim 1, wherein said providing includes calculating a difference value between an associated value of each gene in a first of the sets or a value derived therefrom and an associated value of that gene in a second of the sets or a value derived therefrom; wherein the parameter is a function of the difference value of that gene.

7. (Previously presented) The method of claim 6, wherein said providing further includes:

generating for each of the plurality of genes a scatter value that quantifies variation in the associated values of that gene within the first and second sets; and wherein said parameter is a function of the scatter value and of the difference value, said parameter defining a relative difference value of that gene.

8. (Previously presented) The method of claim 7, wherein said generating employs the following equation:

$$s(i) = (\{1/a\} \{ \sum_m [x_m(i) - \bar{x}_I(i)]^2 + \sum_n [x_n(i) - \bar{x}_U(i)]^2 \})^{1/2}$$

where gene (i) has associated values $x_I(i)$ and $x_U(i)$ in I th and U th states respectively in the first and second sets of associated values, I and U being positive integers; \sum_m and \sum_n are sums over associated values of gene (i) in states I in the first set and in states U in the second set respectively, where $s(i)$ is the scatter value of gene (i) , and a is a constant.

9. (Original) The method of claim 8, wherein said calculating calculates the parameter $d(i)$ from the following equation:

$$d(i) = [\underline{x}_I(i) - \underline{x}_U(i)]/[s(i) + s_o]$$

where s_0 is a constant, and $x_I(i)$ and $x_U(i)$ are the average values of $x_I(i)$ and $x_U(i)$ respectively in the first and second sets of associated values.

10. (Previously presented) The method of claim 9, said adjusting comprising:
dividing the scatter values or average associated values of the genes into subsets each having a similar range of values, and calculating the standard deviation of each of the parameters within each subset; and

altering value of s_0 until a coefficient of variation of the standard deviations of the parameters among the subsets is minimized.

11. (Previously presented) The method of claim 1, wherein said associated values of the genes are correlated with another variable so that each of said associated values has a corresponding value of the variable, and wherein the parameter is provided using a Pearson correlation coefficient related to a weighted difference between each of the associated values and an average associated value, the variance of the associated values and the variance of the variable, said difference weighted by deviation of the corresponding value of the variable of such associated value from its average value.

12. (Original) The method of claim 11, wherein said variable is continuous.

13. (Original) The method of claim 12, wherein said variable is time.

14. (Previously presented) The method of claim 11, wherein the parameter is selected using the Pearson correlation coefficient and a quantity s_0 that has a value adjusted in said adjusting as follows:

dividing the scatter values or average associated values of the genes into subsets each having a similar range of values, and calculating the standard deviation of each of the parameters within each subset; and

altering value of s_0 until a coefficient of variation of the standard deviations of the parameters among the subsets is minimized.

15. (Previously presented) The method of claim 11, the number of sets of associated values being k, k being a positive integer, wherein said Pearson correlation coefficient r(i) is given by:

$$r(i) = \sum_k [(x_k(i) - \bar{x}(i))[(y_k - \bar{y})] / \sqrt{\sum_k (x_k(i) - \bar{x}(i))^2 \sum_k (y_k - \bar{y})^2}$$

where $x_k(i)$ is the associated value of gene (i) in the kth set of associated values, $\bar{x}(i)$ the average of the associated values of gene (i) in all the sets, y_k the value of the variable corresponding to $x_k(i)$, \bar{y} the average value of y_k in all the sets, and \sum_k is a sum over all values of k.

16. (Original) The method of claim 1, wherein the associated values in each set are classified into two or more subsets with values in each subset having a correlation with one another, and wherein the parameter is selected using a quantity related to variances between the associated values in the subsets of the sets and the variances of the associated values within each subset of the sets.

17. (Original) The method of claim 16, wherein the quantity relates to the sum of variances between the associated values in the subsets of the sets and the sum of variances of the associated values within each subset of the sets.

18. (Previously presented) The method of claim 17, wherein the parameter is selected using the Fisher discriminant and a quantity s_0 having a value which has been adjusted in said adjusting as follows:

dividing the scatter values or average associated values of the genes into subsets each having a similar range of values, and calculating the standard deviation of each of the parameters within each subset; and

altering value of s_0 until a coefficient of variation of the standard deviations of the parameters among the subsets is minimized.

19. (Previously presented) The method of claim 18, wherein the number of subsets of associated values of such set being k, k being a positive integer, and the Fisher discriminant F(i) is given by:

$$F(i) = \sum_k n_k [x_k(i) - \bar{x}(i)]^2 / \sum_k \sum_j [x_j(i) - \bar{x}_k(i)]^2$$

where $x_k(i)$ is an associated value of gene (i) in the k th subset of associated values, $x_k(i)$ the average of the associated values of gene (i) in the k th subset, $x(i)$ the average value of the associated values of gene (i) in all of the subsets, n_k the number of associated values in the k th set, \sum_j a sum over all the associated values of gene (i) in the k th subset, and \sum_k a sum of the associated values of gene (i) over all of the subsets.

20. (Previously presented) The method of claim 1, the sets of associated values referred to as original sets, wherein said deriving includes deriving said expected value by:

permuting, for each of the plurality of genes, the associated values for such gene in the original sets to arrive at a number of different permutations;

classifying the associated values in each permutation of each gene into corresponding permuted sets that are different from the original sets; and

supplying for each permutation a parameter value of each of the genes derived from an associated value of such gene in each of the corresponding permuted sets for such permutation or values derived therefrom.

21. (Previously presented) The method of claim 20, wherein said associated values of the genes are correlated with another variable so that each of said associated values has an associated value of the variable, wherein the permuting permutes the associated values so that at least each of some of the associated values has a different associated variable.

22. (Original) The method of claim 21, wherein the associated values are classified into two or more subsets with values in each subset having a correlation with one another, wherein the permuting permutes the associated values so that at least each of some of the associated values is in a subset different from the subset it is classified into.

23-27. (Cancelled)

28. (Currently amended) A method for analyzing a plurality of original sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus

measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

calculating for each of the plurality of genes a value for a statistical parameter indicating differences between associated values of such gene among the original sets;

ranking the values of the parameter of the genes ;

providing an expected value of such parameter for each rank, wherein said providing includes permuting the associated values in the original sets to arrive at sets different from the original sets for each permutation, deriving a value of such parameter for each permutation, and ranking such values, said expected value for each rank being indicative of extent of variations in the parameter for parameters in said rank introduced by the process;

comparing the calculated and expected values for the parameter of the same rank to identify genes whose associated values differ by an amount of statistical significance among the sets; and

providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

29. (Previously presented) The method of claim 28, wherein said providing comprises:

for each permutation, deriving a value of the parameter for each gene and ranking the genes by their associated parameter values; and

determining the expected value of such parameter for each rank by computing an average value of the parameter of all the permutations having such rank.

30. (Previously presented) The method of claim 29, wherein said comparing comprises identifying a gene as one whose associated values differ by an amount of statistical significance among the sets when the difference for such gene between the calculated value of the parameter of a rank and the expected value of such parameter of the same rank exceeds a threshold.

31-32. (Cancelled)

33. (Original) The method of claim 28, wherein the sets of associated values in each permutation contains approximately an equal number of associated values from each of the original sets of associated values.

34-43. (Cancelled)

44. (Currently amended) A computer readable storage device embodying a program of instructions executable by a computer to perform a method for analyzing a plurality of sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

providing for each of the plurality of genes a parameter that contains information concerning differences in the associated values of that gene among the sets;

adjusting the parameters of the plurality of genes so that variables related to the parameters are substantially independent of variations in scatter values or average associated values of the genes over the sets, said scatter values defined by standard deviation of the associated values in the sets;

deriving an observed value and an expected value of the adjusted parameter for each gene from the sets of associated values, said expected value being indicative of extent of variations in the adjusted parameter introduced by the process;

comparing the observed and expected values of the parameter to identify genes whose associated values differ by an amount of statistical significance among the sets; and

providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

45. (Cancelled)

46. (Currently amended) A computer readable storage device embodying a program of instructions executable by a computer to perform a method for analyzing a plurality of

original sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

- calculating for each gene a value for a statistical parameter indicating differences between associated values of such gene among the original sets;

- ranking the values of the parameter of the genes ;

- providing an expected value of such parameter for each rank, wherein said providing includes permuting the associated values in the original sets to arrive at sets different from the original sets for each permutation, deriving a value of such parameter for each permutation, and ranking such values, said expected value for each rank being indicative of extent of variations in the parameter for parameters in said rank introduced by the process;

- comparing the calculated and expected values for the parameter of the same rank to identify genes whose associated values differ by an amount of statistical significance among the sets; and

- providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

47-57. (Cancelled)

58. (Currently amended) A computer system for analyzing a plurality of sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the system comprises:

- one or more computers;

- one or more computer programs running on the computer(s), performing the following:

providing for each of the plurality of genes a parameter that contains information concerning differences in the associated values of that gene among the sets;

adjusting the parameters of the plurality of genes so that variables related to the parameters are substantially independent of variations in scatter values or average associated values of the genes over the sets, said scatter values defined by standard deviation of the associated values in the sets;

deriving an observed value and an expected value of the adjusted parameter for each gene from the sets of associated values, said expected value being indicative of extent of variations in the adjusted parameter introduced by the process;

comparing the observed and expected values of the parameter to identify genes whose associated values differ by an amount of statistical significance among the sets; and

providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

59. (Cancelled)

60. (Currently amended) A computer system for analyzing a plurality of original sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the system comprises:

one or more computers;

one or more computer programs running on the computer(s), performing the following:

calculating for each gene a value for a statistical parameter indicating differences between associated values of such gene among the original sets;

ranking the values of the parameter of the genes ;

providing an expected value of such parameter for each rank, wherein said providing includes permuting the associated values in the original sets to arrive at sets different from the original sets for each permutation, deriving a value of such parameter for each permutation, and

ranking such values, said expected value for each rank being indicative of extent of variations in the parameter for parameters in said rank introduced by the process;

comparing the calculated and expected values for the parameter of the same rank to identify genes whose associated values differ by an amount of statistical significance among the sets; and

providing a list of genes whose associated values differ by an amount of statistical significance among the sets.

61-64. (Cancelled)

65. (Currently amended) A method for analyzing a plurality of sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

measuring samples to obtain the associated values of the plurality of genes;
providing for each of the plurality of genes a parameter that contains information concerning differences in the associated values of that gene among the sets;

adjusting the parameters of the plurality of genes so that variables related to the parameters are substantially independent of variations in scatter values or average associated values of the genes over the sets, said scatter values defined by standard deviation of the associated values in the sets;

deriving an observed value and an expected value of the adjusted parameter for each gene from the sets of associated values, said expected value being indicative of extent of variations in the adjusted parameter introduced by the process;

comparing the observed and expected values of the parameter to identify genes whose associated values differ by an amount of statistical significance among the sets; and

identifying from the plurality of genes those whose associated values differ by an amount of statistical significance among the sets.

66. (Currently amended) A method for analyzing a plurality of original sets of values associated with a plurality of genes to identify genes whose associated values differ by an amount of statistical significance among the sets, said associated values comprising levels of mRNA or protein, said associated values acquired by a process where biological samples containing said plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples, wherein the method comprises:

measuring samples to obtain the associated values of the plurality of genes;

calculating for each of the plurality of gene a value for a statistical parameter indicating differences between associated values of such gene among the original sets;

ranking the values of the parameter of the genes ;

providing an expected value of such parameter for each rank, wherein said providing includes permuting the associated values in the original sets to arrive at sets different from the original sets for each permutation, deriving a value of such parameter for each permutation, and ranking such values, said expected value for each rank being indicative of extent of variations in the parameter for parameters in said rank introduced by the process;

comparing the calculated and expected values for the parameter of the same rank to identify genes whose associated values differ by an amount of statistical significance among the sets; and

identifying from the plurality of genes those whose associated values differ by an amount of statistical significance among the sets.